RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Diagnosis and Treatment of Bronchiectasis

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Bronchiectasis is the end result of several different diseases that share principles of management. The clinical course usually involves chronic bronchial infection and inflammation, which are associated with progression. The cause of bronchiectasis should always be investigated, particularly when it can be treated. We recommend evaluating etiology, symptoms, bronchial colonization and infection, respiratory function, inflammation, structural damage, nutritional status, and quality of life in order to assess severity and to monitor clinical course. Care should be supervised by specialized units, at least when there is a history of chronic bronchial infection, recurrent exacerbations, or a cause that is likely to respond to treatment. Improving symptoms and halting progression are the goals of management, which is based on treatment of the underlying cause and of acute or chronic infections and on the drainage of secretions. Complications that arise must also be treated. Antibiotic prescription is guided by monitoring how well infection is being controlled, and this is indicated by the color of sputum and a reduction in the number of exacerbations. We recommend inhaled antibiotics when bronchial infection is chronic and does not respond to oral antibiotics or when these cause side effects, or when the cause is *Pseudomonas* species or other bacteria resistant to oral antibiotics. Inhaled administration is also advisable to treat initial colonization by *Pseudomonas* species.

Key words: *Bronchiectasis. Exacerbation. Bronchial colonization. Bronchial infection. Bronchial inflammation.*

Diagnóstico y tratamiento de las bronquiectasias

Las bronquiectasias son el resultado final de enfermedades diferentes que tienen puntos de manejo comunes. Suelen cursar con infección e inflamación bronquiales crónicas que se asocian con progresión. Siempre debe investigarse la etiología, en especial de las tributarias de tratamiento. Para valorar la gravedad y hacer el seguimiento, recomendamos evaluar la etiología, la clínica, la colonización-infección bronquial, la función respiratoria, la inflamación, el daño estructural, el estado nutricional y la calidad de vida. Su atención debería realizarse en unidades especializadas, al menos en casos de infección bronquial crónica, agudizaciones repetidas o etiología susceptible de tratamiento. El tratamiento tiene como objetivo mejorar la clínica y detener la progresión, y se basa en el tratamiento de la etiología, de la infección aguda y crónica, en el drenaje de secreciones y en el tratamiento de las complicaciones. La pauta de administración del antibiótico depende del control de la infección, que se comprueba con el color del esputo y la disminución de las agudizaciones. Recomendamos los antibióticos inhalados en la infección bronquial crónica sin respuesta clínica o con efectos secundarios al antibiótico oral, en la causada por *Pseudomonas,* en la causada por microorganismos resistentes a los antibióticos orales y en la colonización inicial por *Pseudomonas.*

Palabras clave: *Bronquiectasias. Agudización. Colonización bronquial. Infección bronquial. Inflamación bronquial.*

Introduction

Bronchiectasis is the abnormal, irreversible dilatation of the bronchi and is associated with changes in the ciliated epithelium. Bronchiectasis is not itself a disease but rather the result of various processes that share certain aspects of management. A distinction has traditionally been made, however, between cystic and noncystic fibrosis bronchiectasis. The first affects a well-defined population of patients for whom respiratory disease is the main predictor of mortality and care is provided by specialized teams. There has been more research and commercial activity related to cystic fibrosis bronchiectasis, and experts have sought consensus on approaches to management.[1-4] This type, however, represents only a small percentage of all cases.[5] Noncystic fibrosis bronchiectasis, on the other

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hand, affects a heterogeneous population of patients and the etiology is likewise varied. Cases of unknown origin, each with particular characteristics, are also included in this group. Patients are often treated in nonspecialized units, less research has been done or commercial interest expressed, and meetings to seek consensus on management have not been held. The prevalence is unknown and probably varies by population; in the Unites States the estimated prevalence is 53 cases per 100 000 adults and the average annual cost per patient is said to be $13 244.[6] That prevalence is slightly higher than that of chronic obstructive pulmonary disease in that country, and 25% of the bronchiectasis patients there have been found to account for 80% of the total expenditure.

Whatever the cause of bronchiectasis, it leaves patients susceptible to bronchial infections and to an inflammatory response leading to progressive lung damage. Given the chronic, progressive nature of the process, it is important to establish more effective management strategies and to put them into effect as early as possible in the course of disease. The present statement has been prepared because of the absence of guidelines for bronchiectasis in general and because those for the noncystic fibrosis form do not reflect the needs of patients with this condition.[7,8] The aim is to improve, facilitate, and unify the approach to management. The recommendations have been established in accordance with the GRADE system[9] (Grades of Recommendation, Assessment, Development, and Evaluation) shown in Table 1. Whenever the level of scientific evidence is low, the recommendations reflect the consensus of the authors.

Diagnosis

Diagnosis of Bronchiectasis

The clinical picture varies greatly and may involve repeated respiratory infections alternating with asymptomatic periods or with chronic production of sputum (simple mucus or mucopurulent or purulent sputum). Bronchiectasis should be suspected when there has been no exposure to tobacco smoke. Sputum may be bloody or hemoptysis might be recurrent. There may be bronchial hyperresponsiveness and breathlessness in relation to the severity of lung function involvement, pleuritic chest pain when the visceral pleura is affected, or weakness and

TABLE 1
Grading Recommendations and Quality of Evidence According to the GRADE System[9]

Grade of Recommendation	Clarity of Evidence	Implications
Strong recommendation[a] High-quality evidence	Well-performed RCTs or exceptionally well-performed observational studies	Can apply to most patients in most circumstances
Strong recommendation[a] Moderate-quality evidence	RCTs with important limitations or unusually strong evidence from well-performed observational studies	Can apply to most patients in most circumstances
Strong recommendation[a] Low-quality evidence	Evidence for at least 1 critical outcome from an observational study or an RCT with serious flaws or indirect evidence	May change when higher-quality evidence becomes available
Strong recommendation[a] Very-low-quality evidence	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	May change when higher-quality evidence becomes available
Weak recommendation[b] High-quality evidence	Well-performed RCTs or exceptionally well-performed observational studies	May differ depending on circumstances or patients
Weak recommendation[b] Moderate-quality evidence	RCTs with important limitations or observational studies with unusually strong evidence	Alternative approaches may be better for some patients under some circumstances
Weak recommendation[c] Low-quality evidence	Evidence for at least 1 critical outcome from observational studies or RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable
Weak recommendation[d] Very-low-quality evidence	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable

Abbreviations: GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Benefits clearly outweigh harms and burdens, or vice versa.
[b]Benefits are closely balanced with harms and burdens.
[c]Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens.
[d]Major uncertainty in the estimation of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens.

TABLE 2
Causes of Bronchiectasis

Postinfection
Bacteria: necrotizing pulmonary infections
Mycobacteria: tuberculosis, nontuberculous mycobacteria
Viruses: adenovirus, measles
Fungi
Bronchial obstruction
Intrinsic: stenosis from scarring, broncholiths, foreign body, tumor
Extrinsic: diseased lymph nodes, tumor, aneurysm
Immune deficiency:
Primary
Immune deficiency (agammaglobulinemia, common variable immunodeficiency, activation-induced deaminase cytidine, antibody deficits with normal immunoglobulin titers, etc)
Combined immunodeficiency (transmembrane peptide transporter deficiency, etc)
Other (Wiskott-Aldrich syndrome, high immunoglobulin E titer, defective neutrophil function, etc)
Secondary: chemotherapy, transplant, hematologic neoplasm, human immunodeficiency virus infection
Impaired mucociliary clearance
Cystic fibrosis
Primary ciliary dyskinesia
Young syndrome
Inflammatory pneumonitis
Aspiration, gastroesophageal reflux disease
Toxic inhalation (drugs, gases, etc)
Structural airway abnormalities
Tracheobronchomegaly (Mounier-Kuhn syndrome)
Cartilage defects (Williams-Campbell syndrome)
Pulmonary sequestration
Tracheobronchomalacia
Tracheal bronchi
Associated with other diseases
Systemic diseases: rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, Marfan syndrome, relapsing polychondritis, ankylosing spondylitis, sarcoidosis
Inflammatory bowel disease: ulcerative colitis, Crohn disease
Other respiratory diseases: asthma, chronic obstructive pulmonary disease, Swyer-James syndrome
a1-antitrypsin deficiency, yellow nails syndrome
Aspergillosis or allergic bronchopulmonary mycosis
Diffuse panbronchiolitis
Unknown cause

weight loss. Sinusitis may be present, especially if there is cystic fibrosis, primary ciliary dyskinesia, primary immune deficiency, Young syndrome, yellow nails syndrome, or diffuse panbronchiolitis.

The airways may appear normal on examination or there may be crackles, rhonchi, and/or wheezes. In advanced stages the patients may develop clubbing, cachexia, signs of respiratory failure, or cor pulmonale.

Diagnosis is based on high resolution computed tomography (CT) performed without contrast, taking 1-mm slices at 10-mm intervals with the patient holding a deep breath.[10] (Strong recommendation. High-quality evidence.) The extent of bronchiectasis and type (cylindrical, varicose, or cystic) can also be determined by CT. The CT criteria for a diagnosis of bronchiectasis are *a)* direct signs such as bronchial dilatation with a bronchoarterial ratio greater than 1 to 1.5 (signet ring signs), lack of tapering of the bronchi, and visualization 1 cm from the pleura, and *b)* indirect signs such as thickening of the bronchial wall, loss of lung volume, honeycombing, a tree-in-bud pattern, and mucus plugs. CT can also identify the etiology in cases of congenital malformation, situs inversus, tracheobronchomegaly, bronchial obstruction, or emphysema due to low α_1-antitrypsin concentration. Bronchiectases due to tuberculosis occur mainly in the upper lung fields, whereas those caused by allergic bronchopulmonary aspergillosis usually appear in central fields. Small nodules, mainly in the lingula and middle lobe, suggest infection by nontuberculous mycobacteria.

Etiologic Diagnosis

Table 2 shows the causes of bronchiectasis. The frequencies have varied over time in developed countries. While postinfectious causes have declined, underlying diseases that predispose to bronchial infection and inflammation have been implicated with increasing frequency.[5] The cause remains unknown in a fairly high percentage of patients, ranging from 26% to 53% depending on the series.[5] A complete medical history and a CT scan often point to the possible cause of bronchiectasis and suggest which diagnostic tests are still needed.[5] It is important to search systematically for the cause, particularly if a specific treatment might be available,[2,5,11-16] as this has important implications for management and prognosis.[5,12] The following causes should be ruled out whenever bronchiectasis is classified as idiopathic: immune

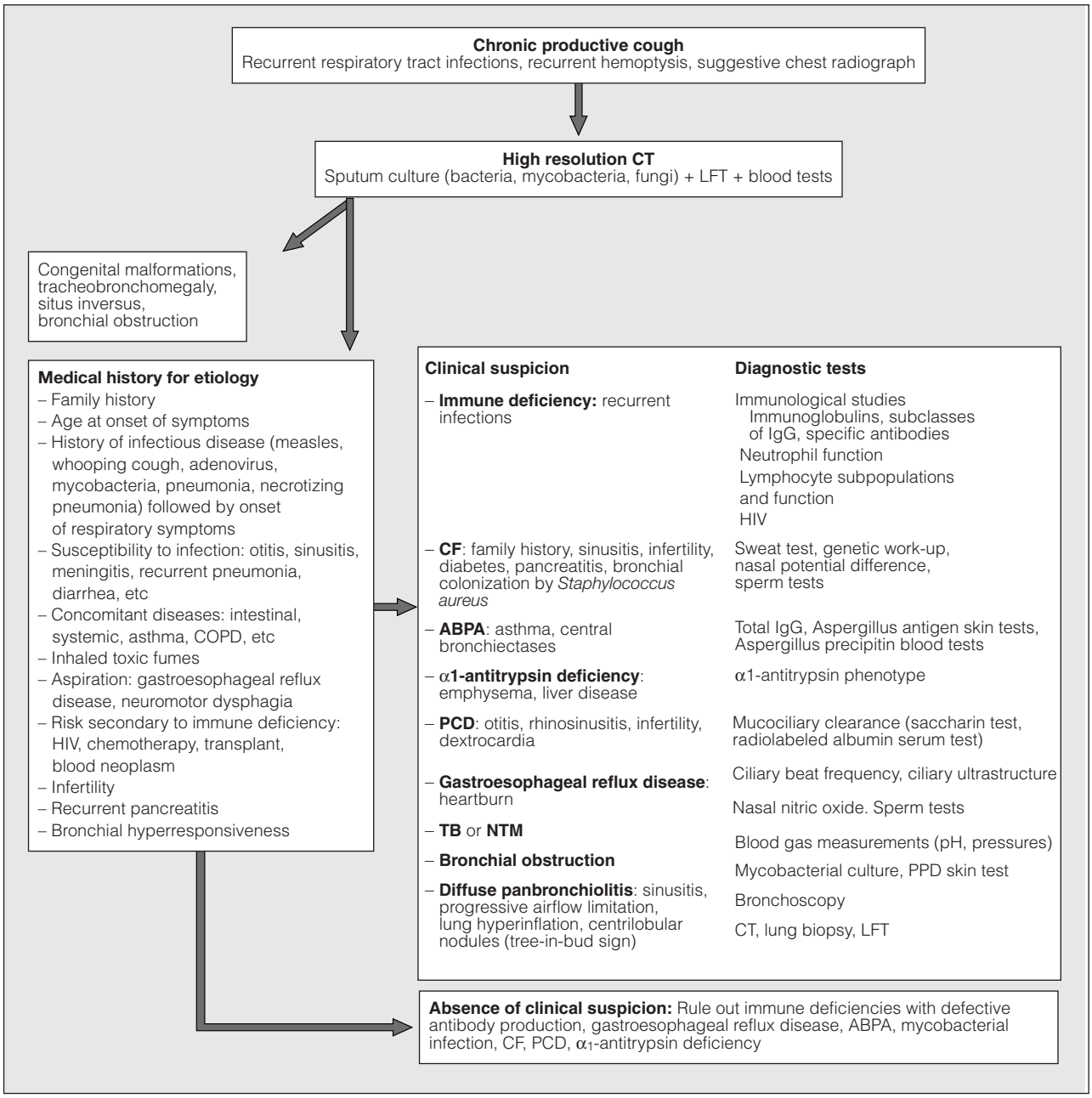

Figure. Diagnostic algorithm. ABPA indicates allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; HIV, human immunodeficiency virus; Ig, immunoglobulin; LFT, lung function tests; NTM, nontuberculous mycobacteria; PCD, primary ciliary dyskinesia; PPD, purified protein derivative RT-23; TB, tuberculosis.

deficiencies with evidence of defective antibody production, gastroesophageal reflux disease, allergic bronchopulmonary aspergillosis, mycobacterial infection, cystic fibrosis, primary ciliary dyskinesia, and α_1-antitrypsin deficiency. (Strong recommendation. High-quality evidence.)

The Figure shows the diagnostic algorithm we propose.

Diagnosis of Exacerbation

Exacerbation is defined as the acute development and persistence of changes in sputum characteristics (increased volume, thicker consistency, greater purulence, or hemoptysis), and/or increased breathlessness unrelated to other causes.[7] An exacerbation may be accompanied by a worsening of cough, fever, asthenia, general discomfort, anorexia, weight loss, pleuritic chest pain, physical changes in the lungs found during examination, x-ray findings suggestive of infection, declining lung function, or elevated markers of systemic inflammation. Exacerbation may be the result of changes in the density of colonizing bacterial flora or the acquisition of a new microorganism.

TABLE 3
Recommended Culture Media, Ideal Incubation Conditions, and Aims

Culture Medium	Incubation Conditions	Comments
Blood agar	35°C, 48 h	May be incubated longer in appropriate humidity (up to 5-7 days for isolation of *Nocardia species*)
Chocolate agar	35°C, 48 h, CO_2	Purpose: isolation of *Haemophilus influenzae* If there is concomitant colonization with *Pseudomonas aeruginosa*, anaerobic incubation is recommended; or use chocolate agar with bacitracin.
MacConkey agar	35°C, 48 h	Selective medium for gram-negative bacilli, including *P aeruginosa*
Sabouraud ± chloramphenicol and Acti-Dione	35°C and 30°C,	Differential media for growing fungi up to 4 weeks
Löwenstein-Jensen or Coletsos media, and enriched selective liquid media	35°C, up to 4 weeks	Purpose: isolation of mycobacteria. The sample should be decontaminated before culture.

A severe exacerbation is one in which there is tachypnea, acute respiratory failure, exacerbated chronic respiratory failure, a significant decline in oxygen saturation or respiratory function, hypercapnia, fever of more than 38°C, hemoptysis, hemodynamic instability, and/or impaired cognitive function.

Diagnosis of Bronchial Colonization, Infection, and Inflammation

Bronchiectases provide the perfect environment for colonization by various microorganisms, as mucociliary clearance of secretions is impaired, thereby facilitating rapid bacterial growth. The bacteria that colonize respiratory mucosa are usually less virulent than those that cause invasive disease and they do not adhere to the bronchial epithelium. However, they are able to develop the means to facilitate their survival, interfering with host defense mechanisms and the actions of antimicrobial agents (through biofilm or capsule formation, or through hypermutability, etc). Bacterial growth occurs on the mucosal surface of airways and does not invade nearby tissues; thus the process involves a "passive" pathogenic effect.[4] The high bacterial inoculation density that is usually reached and processes related to chronic colonization are able to cause an inflammatory effect even in the absence of direct aggression.[4] The distinction between colonization and infection is complicated and it is preferable to refer to bacterial persistence as "pathogenic colonization."[4] However, the following situations can be identified on a clinical level:

1. Bronchial colonization: The presence of a bacterial population that does not trigger an inflammatory response with clinical repercussions other than production of mucus. Three types of such colonization may be distinguished, as follows:

Initial: In stable phase, the first positive culture of a microorganism not isolated in previous cultures.

Intermittent: Positive and negative cultures for the same microorganism separated by at least a month, in patients who are not taking antibiotics against that microorganism. This form is usually chronic, with few or undetectable numbers of colony forming units.[4]

Chronic: Three or more positive cultures for the same microorganism in succession within 6 months and in samples collected at least 1 month apart.[4]

2. Chronic bronchial infection: The presence of a bacterial population that triggers an inflammatory response with persistent production of purulent sputum.[17] Recurrent respiratory infections with systemic repercussions—fever, asthenia, and/or weight loss—may be present.

The diagnosis of such colonization or infection is based on clinical manifestations and culture of respiratory secretions. A finding of anti-*Pseudomonas* species antibodies may help identify chronic colonization by these microorganisms, particularly in cystic fibrosis patients with bronchiectasis, but assays do not have advantages over bacterial culture.

3. Bronchial inflammation: Nonspecific bronchial response to infection that aims to eliminate the microorganism. When the microorganism cannot be cleared, inflammation becomes chronic, a large number of white blood cells collect and these are responsible for purulent secretions[17] and associated with lung injury. The inflammatory response may be local[18] or systemic.[19] A local response is evident from the color of sputum: white mucus contains few inflammatory cells, light green or yellow sputum is mucopurulent and contains a moderate number, and dark green sputum is purulent and contains a large number.[17] Analysis to quantify inflammatory markers in respiratory secretions[18] is not undertaken systematically. Systemic inflammation can be measured by quantifying white blood cells and neutrophils, the erythrocyte sedimentation rate, and levels of C-reactive protein and immunoglobulin A.[11,19]

Microbiology of Respiratory Samples: Assessment of Resistance

The preferred sample for microbiology is sputum that has been inspected under a microscope to rule out contamination by upper airway secretions (>25 leukocytes and <10 epithelial cells per low power field). Culturing on both standard and selective media is recommended to increase yield and assist in the identification of distinct microorganisms (Table 3).

The systematic analysis of bacterial counts is controversial because of the time it requires and the degree of usefulness of the data obtained, but such counts are recommended for the evaluation of new treatments, including combinations of antimicrobial agents. If colonization or infection by *Nocardia* species is suspected,[20] the microbiologist should be told. A sputum Gram stain before culturing will be useful, as will the inclusion of selective media and the establishment of incubation conditions that will ensure isolation of these species.

Distinct morphotypes of the same microorganism, with the same or different patterns of antimicrobial sensitivity, may appear in colonies; an antibiogram should therefore be obtained. Chronic infection, elevated counts, selective pressure from antimicrobial agents, and the unfavorable pharmacokinetics of some antibiotics in respiratory mucosa facilitate the development of resistance. Some pathogens isolated have shown an unusually high number of resistant mutations (10 to 1000 times the usual rate), which, along with a high inoculation density, can favor the selection of resistant strains.[21]

Although an antibiogram is essential for guiding treatment, conventional in vitro sensitivity does not always correlate with therapeutic response, as happens with microorganisms able to form a biofilm, where the activity of many antibiotics is diminished.[22] When an antimicrobial agent is to be administered by nebulizer, however, the interpretation of the antibiogram should be adjusted to take into consideration that this form of delivery achieves much higher concentrations of antibiotic in the bronchial mucosa.[23]

Nontuberculous mycobacteria should be cultured in appropriate media and the microbiologist must be expressly asked to establish conditions that ensure these microbes will be isolated. The sample should be decontaminated to eliminate other bacteria and possible fungi (Table 3). A stain for acid-fast bacilli (Ziehl-Neelsen or, preferably, a fluorescent stain with auramine) may be useful, but genome amplification should be used to rule out the presence of *Mycobacterium tuberculosis*. (Strong recommendations. Moderate-quality evidence.)

Assessment of Severity, Follow-up, and Prognosis

Bronchiectasis is chronic, irreversible, and progressive. The prognosis depends on the underlying disease, the extent of tissue damage, the impact on respiratory function, and the severity of exacerbations.[1] Chronic bronchial infection, particularly by *Pseudomonas* species, severe exacerbations, and systemic inflammation are associated with disease progression.[24] The early diagnosis of bronchiectasis, the diagnosis and treatment of the cause, adequate treatment of chronic bronchial infection, regular check-ups, and preventive measures can delay disease progression and improve survival.[1] When bronchiectasis is the result of a process for which a specific treatment is available[1,2,11-16] or when there is chronic bronchial infection and/or recurrent exacerbation, medical and nursing care should be carried out by specialized teams.

Aspects that must be taken into consideration and monitored in order to assess severity and initiate early treatment that can minimize morbidity and mortality are as follows:

Etiology. Consider whether the cause of bronchiectasis is still present, whether it is being adequately treated, and what impact the bronchiectasis has on the underlying disease. The progression of bronchiectasis is the main cause of morbidity and mortality in patients with cystic fibrosis or immune deficiencies, and in such cases treatment and follow-up should be more aggressive.[1,12,15]

Clinical picture. Check-ups should be scheduled about every 1 to 6 months, depending on morbidity, severity, and progression. The color and volume of sputum in stable phase should be checked: when the sputum contains more mucus, there will be less inflammation.[17] The number and severity of exacerbations must also be checked because more episodes of greater severity are associated with greater decline in lung function.[24] Investigate shortness of breath, signs and symptoms of bronchial hyperresponsiveness, the frequency and intensity of hemoptysis, and evidence of systemic involvement (asthenia, weight loss, persistent fever). Perform a physical examination of heart and lungs.

Bronchial colonization-infection. Take a sputum sample for culture and order an antibiogram at each check-up and for each exacerbation episode. The microorganisms that most often colonize bronchiectases are nontypeable *Haemophilus influenzae* and *Pseudomonas aeruginosa.*[18] *Staphylococcus aureus* is the most common colonizer in patients with cystic fibrosis and allergic bronchopulmonary aspergillosis; when this pathogen is isolated in other patients, they should be reassessed to rule out those etiologies.[25] It is important to detect and eradicate *Pseudomonas* species early, as this is very difficult once infections is established. Measures to prevent the transmission of infection by multidrug resistant strains between patients must be in place. Nontuberculous mycobacteria are being isolated increasingly often, and so cultures for these germs should be obtained annually and whenever there is unexplained clinical deterioration.[26] Fungal colonization may develop at advanced stages of the disease but has no pathogenic repercussions in most cases. An exception is colonization by *Aspergillus fumigatus*, which can cause allergic bronchopulmonary aspergillosis; its presence should be investigated annually.

Effects on respiratory function. Lung function should be evaluated with a postbronchodilator spirometry test at least once a year and at each visit oxyhemoglobin saturation should also be measured. Arterial blood gases should be analyzed and, depending on severity of lung function impairment, a stress test (6-minute walk test) should also be performed. Patients at risk of rapid deterioration should undergo spirometry at each visit. Progressive airflow limitation is the main finding, related to thickening of the bronchial wall, and forced expiratory volume in 1 second (FEV_1) is the most important predictor of mortality. The degree of lung function decline is greater in patients with chronic *Pseudomonas* infection[24,27] and more marked systemic inflammation,[24] but decline is less severe if proper treatment is provided.[27,28]

Systemic inflammation. An annual blood test should include a complete blood count and assessment of the

erythrocyte sedimentation rate and levels of inflammatory markers, including C-reactive protein and immunoglobulin A. Markers of nutritional status should also be investigated, especially in patients with chronic bronchial infection. Other more specific tests may be ordered based on clinical suspicion (eg, specific immunoglobulin E when allergic bronchopulmonary aspergillosis is suspected).

Structural damage. High resolution CT is more sensitive than lung function tests for detecting structural changes and progression.[12] The decision to order additional imaging studies should be based on balanced consideration of the information they can provide and the repeated exposure to radiation. CT every 2 years is recommended for patients at high risk of progression, provided new lesions are appearing in the chest x-ray.[27] An x-ray is recommended when acute pulmonary complications (hemoptysis, pneumonia, pneumothorax, etc) are suspected.

Nutrition. Evaluation of nutritional status should be included in the follow-up of patients with bronchiectasis given the risk of malnutrition. Various approaches are possible, depending on availability.[29] At each visit or admission, weigh the patient and calculate body mass index (BMI) and weight loss over time. The minimum recommended BMI is 22 kg/m^2 for women and 23 kg/m^2 for men. A BMI less than 18.5 kg/m^2 and/or weight loss of more than 5% in 2 months or 10% in 6 months should be considered clear evidence of malnutrition. It is recommended to undertake a detailed annual assessment of diet (using a 3-day intake questionnaire), albumin (on hospitalization and at least once a year), and prealbumin (especially in hospitalized patients or those experiencing exacerbation in order to evaluate the efficacy of nutritional treatment). A more complete nutritional evaluation should be done in a specialized nutrition department if the patient is malnourished or at risk.

Quality of life. The validated St George's Respiratory Questionnaire assesses the patient's perception of severity, which is influenced most by FEV_1, and sputum volume.[30]

Therapeutic Recommendations

The aim of treatment is to improve the patient's clinical situation and prevent disease progression.

Etiologic Treatment

Treatment that targets the underlying cause of bronchiectasis should be given whenever the etiology is known, especially in patients with defective antibody production,[12] allergic bronchopulmonary aspergillosis,[5] gastroesophageal reflux disease,[5] airflow limitation, infection by mycobacteria,[26] α_1-antitrypsin deficiency, cystic fibrosis,[1,15] and concomitant diseases[5] (inflammatory bowel disease, autoimmune diseases, panbronchiolitis, etc). (Strong recommendation. High-quality evidence.)

Treatment for Exacerbation

Antibiotic therapy, elimination of secretions, and the treatment of associated bronchospasm are the bases of the approach to managing exacerbations. The choice of antibiotic depends on whether or not chronic colonization or infection of the bronchi has been documented. If there is colonization, choice of antibiotic therapy should be guided by previously isolated microorganisms. If there is infection, antibiotics should be prescribed empirically. Take into consideration the risk of colonization by *P aeruginosa* (related to recent antibiotic therapy or hospitalization, serious disease, or prior isolation of *Pseudomonas* species.[7]) The antibiotic should be changed in accordance with the microorganism isolated from sputum collected during the exacerbation, based on an antibiogram. Antibiotics that penetrate respiratory secretions well should be used at high dosages. They should be administered until the sputum is no longer purulent or for at least 10 days. In cases of *Pseudomonas* infection, intake should continue for 14 to 21 days.[2,4] The place and route of administration will depend on the severity of the exacerbation and the presence or not of chronic bronchial infection by multidrug resistant microorganisms. Mild exacerbations can be treated orally on an outpatient basis.[2] Intravenous delivery is required for severe exacerbations, chronic bronchial infection by microorganisms resistant to oral antibiotics, patients with cystic fibrosis with exacerbations due to *Pseudomonas* species when this microorganism has not been previously isolated, and whenever there is no response to oral antibiotic therapy.[4] An intravenous drip may be provided in hospital or at home, depending on the patient's status and the resources available, always provided there is appropriate supervision.[31] For moderate-to-severe exacerbations due to *Pseudomonas* species, prescription of 2 intravenous antibiotics is recommended; generally these will be a β-lactam antibiotic and an aminoglycoside.[2,4] The latter is best administered in a single dose.[32] Adding an inhaled antibiotic to an oral or intravenous one has not been shown to provide clinical benefits.[33] (Table 4). (Strong recommendations. Moderate-quality evidence.)

Treatment of Bronchial Colonization and Infection (Table 4)

Initial bronchial colonization. No evidence supports antibiotic treatment of initial colonization except in cystic fibrosis patients with bronchiectasis when the pathogen in question is *Pseudomonas* species.[4] The aim is to eradicate the colony before it becomes chronic. Oral ciprofloxacin and an inhaled antibiotic (tobramycin or sodium colistimethate) should be taken for 3 weeks. Inhaled treatment should continue for 3 to 12 months.[4,34] An alternative treatment would be to administer 2 intravenous antibiotics for 14 to 21 days, followed by an inhaled antibiotic for 3 to 12 months (Table 4). (Strong recommendation. Moderate-quality evidence.)

Although no studies of other etiologic contexts have been published, it is recommended to administer oral ciprofloxacin for 3 weeks and, if eradication is not achieved, to apply the same protocol as for cystic fibrosis. Assessment of the situation should be tailored to the individual situation when other microorganisms are isolated. (Strong recommendation. Low-quality evidence.)

TABLE 4
Antibiotic Therapy in Different Clinical Situations[a]

Situation	Remarks	First Line Treatment	Alternative Treatment	Duration
Exacerbation	Empirical. Cover previously isolated microorganisms. Modify based on sputum culture			10-21 d (except azithromycin, which is recommended for 3-5 d)
	1. Mild exacerbation			
	Haemophilus influenzae	Amoxicillin-clavulanic acid: 875/125 mg every 8 h, oral	Amoxicillin: 1-2 g/8 h, oral; ciprofloxacin: 750 mg/12 h, oral; or azithromycin: 50 mg/24 h, oral	
	Staphylococcus aureus	Cloxacillin: 500-1000 mg/6 h, oral	Amoxicillin-clavulanic acid: 875/125 mg/8 h, oral	Levofloxacin: 750 mg/24 h, oral
	Pseudomonas species	Ciprofloxacin: 750 mg/12 h, oral	Levofloxacino: 750 mg/24 h, oral	
	2. Severe exacerbation, or poor response to oral antimicrobial therapy			
	Haemophilus influenzae	Amoxicillin-clavulanic acid: 1-2 g/8 h, IV	Ceftriaxone: 2 g/24 h, IV	
	Pseudomonas species	Ceftazidime: 2 g/8 h, IV + tobramycin: 5-10 mg/kg/24 h, IV, or amikacin: 15-20 mg/kg/24 h, IV	Imipenem: 1 g/8 h, piperacillin-tazobactam: 4 g/8 h; aztreonam: 2 g/8 h; ceftazidime: 2 g/8 h; meropenem: 2 g/8 h; or ciprofloxacin[d]: 400 mg/12 h, IV + amikacin: 15-20 mg/kg/24 h, IV	
Initial colonization (mucus production)	*Pseudomonas* species	Ciprofloxacin: 750 mg/12 h, oral + tobramycin: 300 mg/12 h, inhaled; or sodium colistimethate: 1-2 mU/12 h, inhaled[b]	IV treatment with 2 drugs + tobramycin: 300 mg/12 h, inhaled; or sodium colistimethate: 1-2 mU/12 h[b], inhaled	3 wk
		Continue taking an inhaled antibiotic	Continue taking an inhaled antibiotic	3–12 mo
Chronic bronchial infection (purulent sputum)	*H influenzae*	Amoxicillin-clavulanic acid: 875/125 mg every 8 h, oral	Ciprofloxacin: 750 mg/12 h, oral; or amoxicillin: 1-2 g/8 h, oral	Prolonged. It depends on the infection control (maintenance of the purulent sputum)
	S aureus	Cloxacillin: 500-1000 mg/6 h, oral	Amoxicillin-clavulanic acid: 875/125 mg/8 h, oral	
	Pseudomonas species	Tobramycin: 300 mg/12 h, inhaled in cycles of 28 d on and off[c]; or sodium colistimethate: 1-2 mU/12 h, inhaled[b]		
	Burkholderia cepacia	Co-trimoxazole: 160/800 mg/12 h, oral	Doxycycline: 100 mg/12 h, oral; or tobramycin: 300 mg/12 h, inhaled in cycles of 28 d on and off[c]	
	Stenotrophomonas species	Co-trimoxazole: 160/800 mg/12 h, oral	Doxycycline: 100 mg/12 h, oral	

Abbreviation: IV, intravenous.
[a]The antibiotics named are the most often prescribed. Choice of these or others, or of combinations, will depend on what microorganism is isolated and on the antibiogram. The dosages mentioned are those recommended for adults.
[b]The dosage of sodium colistimethate will depend on the type of nebulizer used. A nebulizer with a smaller residual volume, such as I-neb, will allow for using a smaller dose (1 mU/12 h).
[c]Consider administering oral ciprofloxacin or an inhaled antibiotic during periods of rest in cases of difficult-to-control bronchial infection.
[d]Ciprofloxacin should be administered orally. Other combinations can be used, on the basis of information from the antibiogram.

Intermittent or chronic bronchial colonization. Consider prolonged antibiotic therapy in any of the following situations: recurrent exacerbations, early relapse, hospitalization, declining lung function, or chronic colonization by *Pseudomonas* species. Apply the same protocols as for chronic bronchial infection. (Strong recommendation. Low-quality evidence.)

Chronic bronchial infection. Treatment is based on prolonged use of antibiotics[35] and drainage of secretions. The aim is to break the vicious cycle of infection and inflammation by reducing both the bacterial load and the inflammatory response, and along with them the sputum volume and purulence, the number and severity of exacerbations, and lung function decline. The choice of antibiotic depends on the microorganism responsible for infection and the antibiogram. The treatment protocol and duration depend on how well the infection is brought under control, as evidenced by a sputum appearance that is kept as white as possible and by fewer exacerbations. Treatment may be oral or inhaled. An inhaled antibiotic is recommended when the patient does not respond to oral administration or there are adverse effects and when infection is by *Pseudomonas species*[1-4,28,36] or microorganisms resistant to antibiotics given orally.[37] The antibiotics that are available are sodium colistimethate and tobramycin without an adjuvant. If other antibiotics are required, an intravenous preparation can be considered. These should be as isotonic as possible and without additives[37] (amoxicillin, ceftazidime, aztreonam), although few studies provide evidence of the effectiveness of that approach. Given that tobramycin alone is administered intermittently, in 28-day periods followed by 28 days off treatment,[28] another antibiotic, oral or inhaled, might be required by patients with difficult-to-control bronchial infection during off periods. Inhaled antibiotics should be administered with specifically designed nebulizers, such as the PARI LC PLUS (Pari), which has a high-flow compressor,[28,33,36] or with electronic nebulizers such as the eFlow (Pari) or the I-neb (Respironics). They may cause bronchospasm, increase dyspnea, or produce chest discomfort which must be controlled. A bronchodilator with rapid onset of action should be on hand, and secretions should be drained before the antibiotic is inhaled. Aminoglycosides should be avoided in patients with hearing loss or renal insufficiency (Table 4). (Strong recommendations. Moderate-quality evidence.)

Treatment of Bronchial Inflammation

Prolonged treatment with oral corticosteroids or ibuprofen is not recommended due to adverse effects.

Macrolides. Macrolide agents are effective in the treatment of diffuse panbronchiolitis and they reduce the number of exacerbations in patients with bronchiectasis from other causes.[38,39] The effect is probably due to modulation of the inflammatory response and the ability of these antibiotics to impede biofilm formation. Macrolides are recommended in chronic bronchial infection by *Pseudomonas* species[1,38] or other microorganisms that are difficult to control in spite of adequate treatment.[39] The drug for which the most experience has accumulated is azithromycin, which is taken in weight-adjusted dosages of 250 to 500 mg 3 days per week for periods ranging from 3 to 6 months. Studies demonstrating its efficacy and safety over treatment periods of 12 months have not been published and the ideal regimen (duration, dosage, interval) is yet to be established. Liver function should be checked in the early weeks of treatment and every 6 months thereafter. The presence of nontuberculous mycobacteria in respiratory secretions should also be investigated before treatment is started and every 6 months. Macrolide monotherapy should not be prescribed if nontuberculous mycobacteria have been isolated.[26] (Strong recommendations. Moderate-quality evidence.)

Inhaled corticosteroids. These drugs are indicated in patients with bronchial hyperreactivity.[40] They have been shown to be effective in patients producing large volumes of sputum,[41] although it is recommended that they be considered on an individual basis rather than prescribed systematically.[40,41] (Strong recommendation. Moderate-quality evidence.)

Treatment of Bronchial Hyperresponsiveness

Bronchodilators and inhaled corticosteroids will be prescribed for bronchial hyperresponsiveness. Bronchodilators also improve ciliary motility and facilitate clearance of secretions. Short-acting bronchodilators should be administered before physical therapy sessions and before antibiotic aerosol therapy.[3] (Strong recommendations. Moderate-quality evidence.)

Nutritional Treatment

Nutritional recommendations should be offered on an individual basis as soon as possible with the aim of improving energy intake, particularly in patients with severe disease or at greater risk of malnutrition.[29] Diet supplements are advisable for persons with a BMI under 20 kg/m^2 or for others who are losing weight rapidly (especially during exacerbations and hospitalization). High-energy, polymeric enteral diets should be prescribed, especially if fluids must be restricted. In situations of high metabolic stress (albumin values of <3 g/dL) the oral intake supplements should also be high in proteins. Normally, formulas with high fat content should not be prescribed. When the patient has diabetes, formulas high in monounsaturated fatty acids improve metabolic control.[42] (Strong recommendations. Low-quality evidence.)

Pulmonary Rehabilitation and Mucolytic Agents

Patients should be enrolled in pulmonary rehabilitation programs supervised by specialists in order to facilitate the elimination of secretions and improve exercise tolerance and health-related quality of life.[42] Both outpatient and hospital-based measures are effective for preventing cross infections and maintaining adequate oxygenation in patients with moderate to severe disease. (Strong recommendation. Moderate-quality evidence.)

Respiratory physiotherapy. Respiratory physiotherapy once or 3 times per week is recommended for patients with bronchial hypersecretion (≥30 mL/d).[42] Sessions should be given after bronchodilator treatment and before administration of inhaled antibiotics.[3] Treatments include a variety of techniques that can be combined (Table 5). There is no evidence as to which approaches are more effective and decisions will depend on the patient's age and ability to carry out the maneuvers. Techniques that can be self-administered are recommended to facilitate long-term adherence. (Strong recommendations. Low-quality evidence.)

Exercise. Aerobic physical exercise (walking, running, cycling, or swimming) improves tolerance and health-related quality of life. In addition to the respiratory physiotherapy techniques, all patients should take moderate to intense exercise for 30 minutes on 3 or 4 days per week; alternatively, moderate exercise every day can be undertaken.[43] (Strong recommendation. Moderate-quality evidence.)

Mucolytic agents. Bromhexine or mannitol can facilitate the clearance of secretions.[44,45] A nebulized hypertonic saline solution and deoxyribonuclease can reduce the number of exacerbations in cystic fibrosis patients with mild or moderate respiratory symptoms.[1] (Strong recommendation. Moderate-quality evidence.) In bronchiectasis arising from other causes, deoxyribonuclease has not been shown to be effective[46]; however, maintaining good hydration with a nebulized hypertonic saline solution can be beneficial.[45]

Treatment of Complications

Hemoptysis. Usually present in an exacerbation, hemoptysis requires administration of an intravenous antibiotic in addition to ordinary management steps. Inhaled treatments and physiotherapy should be avoided, at least during the first 24 to 48 hours. The embolization of bronchial arteries in the area where bleeding occurs is the treatment of choice. Surgery is only indicated in life-threatening situations, provided the source of bleeding is known and hemoptysis cannot be controlled by the aforementioned measures.[2,47] (Strong recommendation. Moderate-quality evidence.)

TABLE 5
Techniques to Improve Mucociliary Airway Clearance

Assisted techniques
Conventional respiratory physiotherapy (bronchial drainage, effective cough, chest percussion and vibrations)
Active cycle of breathing techniques
Autogenic drainage
Slow expiration with the glottis open in lateral position
Airway oscillation device: intrapulmonary percussion ventilator
Unassisted techniques
Airway oscillation devices: Flutter, Cornet, Acapella
Forced expiration (huff)
Positive expiratory pressure
High-frequency thoracic compression

Amyloidosis. Chronic inflammation increases the production of amyloid A in the liver. This acute-phase reactant is broken down by circulating macrophages, after which the degradation products are deposited in tissues. Diagnosis requires biopsy of the affected organ. Urine analysis can be used for screening, as 95% of patients with amyloidosis have proteinuria. The affected organ and chronic infection and inflammation must all be treated. (Strong recommendation. Moderate-quality evidence.)

Respiratory failure. Oxygen therapy and noninvasive ventilation should be provided in case of acute or chronic respiratory acidosis. Indications for lung transplantation are FEV_1 less than 30% of predicted or rapid loss of function in patients with severe bronchiectasis, chronic respiratory failure, hypercapnia, pulmonary hypertension, exacerbations, or frequent serious complications.[48] Colonization by multidrug resistant microorganisms is a relative contraindication.

Surgery

The only curative treatment for localized bronchiectasis that is difficult to manage will be surgery, provided an underlying causative disease has been ruled out. Surgery is indicated for palliative purposes when there is severe hemoptysis with ineffective embolization or areas with abscesses that cannot be cured with antibiotic treatment.[49] (Strong recommendation. Low-quality evidence.)

Criteria for Hospitalization

Admission is considered in cases of severe exacerbation, lack of improvement with outpatient care, requirement for intravenous treatment, progressive lung function decline, uncontrolled progressive weight loss, comorbidity, lack of social support, moderate to severe hemoptysis, or other complications. Criteria for admission to an intensive care unit are the same as for other respiratory diseases.[7] Measures to prevent cross infection should be put in place.

Prevention of Infections

Follow guidelines for preventing lower respiratory tract infections.[7] Patients should be vaccinated against influenza and pneumococcal infection. (Strong recommendations. Low-quality evidence.)

Patient Education

Bronchiectasis is a chronic disease and its management can be complex. Patients should be followed in a specialist respiratory medicine unit with a pulmonologist and expert nursing staff if their condition can benefit from specific etiologic treatment[1,2,11-16] or if they have chronic bronchial infection and/or recurrent exacerbations. Education and supervision should deal with how to recognize an exacerbation and provide initial self-management,[50] how to administer inhaled and intravenous antibiotics at home, and how to keep equipment clean. Other areas to cover are the administration of oxygen therapy and mechanical

ventilation and vaccines, as well as nutrition, physiotherapy, and adherence to prescribed treatments. (Strong recommendation. Moderate-quality evidence.)

Aspects to Consider in Children

Many cases of adult bronchiectasis begin in childhood,[5] and early intervention therefore has the potential to minimize morbidity and mortality. Immunologic immaturity may be an important factor encouraging bronchiectasis, as most childhood cases are acquired through infections. The bacteriologic pattern is different from that of the adult; *H influenzae* and *Streptococcus pneumoniae* are the most frequently implicated pathogens, but the isolation of *P aeruginosa* is not uncommon and calls for ruling out cystic fibrosis.

Bronchiectases that develop just after pneumonia may disappear,[51] leading some authors to suggest new definitions for childhood disease which would distinguish the following types: *a)* early pre-bronchiectasis (persistent bronchial inflammation without structural changes), a condition that might resolve, persist, or progress to *b)* bronchiectasis detected by CT in which bronchial dilatation is evident and which may also resolve, persist, or progress to *c)* established bronchiectasis, which would be irreversible.

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